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Patent

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: BUECHLER et al.

Title: NOVEL METHODS FOR THE
ASSAY OF TROPONIN I AND T
AND COMPLEXES OF
TROPONIN I AND T AND
SELECTION OF ANTIBODIES
FOR USE IN IMMUNOASSAYS

Appl. No.: 09/349,194

Filing Date: July 7, 1999

Examiner: Gail Gabel

Art Unit: 1641

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December 13, 2002
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RESPONSE TO OFFICE ACTION

Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action dated September 6, 2002 ("Paper No. 22"), Applicants respectfully requests reconsideration of the claimed invention in view of the following remarks.

The present invention relates to the assay of free and complexed troponin isoforms in patient samples. Specifically, the invention describes assay methods and kits that comprise antibodies specific for various cardiac troponin forms. Assays may use an antibody or antibody cocktail that binds to one or more specific troponin form, or that binds all forms. The assay methods and kits of the present invention can be used to diagnose unstable angina and/or

myocardial infarction for example. Claims 85-96, 102-106, and 114-142 are presently pending in the instant application. A copy of the pending claims is attached hereto as Appendix A for the convenience of the Examiner.

35 U.S.C. § 112, first paragraph, enablement requirement

Applicants respectfully traverse the rejection of claims 85-96, 102-106, and 114-142 under 35 U.S.C. § 112, first paragraph, in which the Examiner contends that the specification does not enable the skilled artisan to provide a single antibody having a binding specificity for each of free cardiac specific troponin isoform, binary complexes comprising cardiac specific troponin isoform(s), and ternary complexes comprising cardiac specific troponin isoform(s). Applicants submit that the skilled artisan could practice the claimed invention without undue experimentation.

As an initial matter, the Examiner acknowledges that the specification is enabling for assays to determine free and complexed cardiac specific isoforms of troponin using a cocktail of antibodies to provide the necessary binding specificity. In this regard, Applicants point out that claims 134-142 recite the use of an antibody cocktail in the claimed assays.

With regard to the substance of the enablement rejection, Applicants respectfully disagree that "there is no predictability based on the instant specification that the presence or amount of all of the free, binary and ternary complexed isoforms of [cardiac specific troponin] in a sample can be determined using an antibody [having] specific binding for each and all of the free, binary and ternary complexed isoforms." Paper No. 22, page 4. As an aid to the Examiner in this regard,

Applicants provide herewith a declaration of Dr. Kenneth F. Buechler, describing why those of ordinary skill in the art would readily acknowledge that such antibodies could be produced using only routine methods well known in the art.

As described in paragraph 4 of the Buechler declaration, cardiac specific troponin isoforms of Troponin I and T each contain certain antigenic sites that are "cardiac specific," and antibodies directed to these sites may be used to determine cardiac specific troponin isoforms from non-cardiac troponin isoforms. As further described in paragraphs 5 and 6, certain of these cardiac specific sites may be obscured in binary and ternary complexes of the cardiac specific troponin isoforms, and thus antibodies to these sites may be specific to the free form or to the binary complex form of the troponin isoform.

Certain other cardiac specific sites, however, may remain available for antibody recognition even in complexes comprising the troponin isoform. Such sites can provide an epitope through which a single antibody can provide specific binding for each and all of the free, binary and ternary complexed isoforms. As noted by Dr. Buechler in paragraph 7 of the declaration, this point is clearly brought home to the skilled artisan in the instant specification, e.g., on page 24, lines 21-29.

Applicants also respectfully disagree that "the specification fails to provide any guidance to enable the claimed method to make and use an antibody that specifically binds all of the free, binary and ternary complexed isoforms." Paper No. 22, paragraph bridging pages 4 and 5. In fact, the specification describes methods for obtaining antibodies that are insensitive to the complex

state of cardiac specific troponin isoforms, *e.g.*, on page 21, line 3, through page 22, line 19. As described in this section, purified troponin complexes may be used as immunogens in mice or rabbits to prepare monoclonal or polyclonal antibodies, which may be screened for complex-insensitive antibodies for use in the claimed assay methods.

Applicants also respectfully disagree that "[t]here are no working examples that show... results using an antibody, which is encompassed by the broad scope of the claims. As discussed by Dr. Buechler in paragraph 8 of the declaration, Example 10 describes certain antibodies that were demonstrated to bind both free and binary complexes of cardiac specific troponin I equally well. *See, e.g.*, specification, page 63, lines 20-26. Applicants note that a single biotinylated antibody, and a single labeled antibody, are used in these assays, which rely on formation of a sandwich of (labeled antibody)-(analyte)-(biotinylated antibody)-(avidin solid phase) for development of an assay signal. Specification, page 62, lines 20-24. The skilled artisan would understand that both the biotinylated and labeled antibodies must each bind to both free and binary complexes of troponin I in order for the described assays to measure both free and complexed troponin I forms.

Similarly, in Example 17 on page 76, the specification describes an assay able to measure both free and ternary complexes of troponin T. As noted on lines 7-9 and 27-29, the biotinylated anti troponin T peptide 3 antibody is used to formulate such an assay. Again, the skilled artisan would understand that the biotinylated antibody must bind to both free and ternary complexes of troponin T in order for the described assay to measure both free and complexed troponin T forms.

Applicants further disagree that the quantity of experimentation necessary would be undue. Paper No. 22, page 5. As noted by Dr. Buechler in paragraph 3 of the declaration, methods for identifying antibodies that are insensitive to the complex state of cardiac specific troponin isoforms are described in detail in the instant specification. Moreover, as noted by the Examiner, the level of skill in the art for producing antibodies and formulating assay methods is high. Paper No. 22, page 5.

Considering the teachings of the specification, Dr. Buechler concludes that the skilled artisan could indeed provide a single antibody population having a binding specificity for each of free cardiac specific troponin isoform, binary complexes comprising cardiac specific troponin isoform(s), and ternary complexes comprising cardiac specific troponin isoform(s), using only the teachings of the instant specification as filed, together with methods that are routine and well known in the art. *See, e.g.*, Buechler declaration, paragraph 3.

In view of this objective evidence of enablement, and the foregoing discussion of the various Wands factors cited by the Examiner in the office action, Applicants respectfully submit that one of ordinary skill in the art could make and use the claimed invention using the specification as a guide without undue experimentation. Applicants, therefore, request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any